Human Surveillance Activities Plan

I. Introduction

Arthropod-borne viruses (arboviruses) are transmitted to people by the bite of an infected arthropod, typically a mosquito or tick. Arboviruses can cause asymptomatic infections or a clinical illness that ranges in severity from a self-limited febrile illness to a severe neurologic illness with high fever, malaise, photophobia, meningitis, encephalitis, coma or death.

Arboviral infections of importance in Virginia include Eastern Equine Encephalomyelitis (EEE), St. Louis Encephalitis (SLE), the California encephalitis group, particularly La Crosse (LAC), West Nile fever (WNF), and West Nile neuroinvasive disease (WNND), formerly West Nile encephalitis and meningitis.

Eastern Equine Encephalomyelitis (EEE) is primarily of concern in coastal areas, especially when mosquito populations are increased, particularly the species associated with transmission to humans. Reports of equine cases mean the virus is spilling out of the usual mosquito-bird-mosquito cycle and people are at increased risk. Surveillance reports from surrounding states, such as mosquito species, mosquito infectivity, seroconversion of sentinel chicken flocks, disease in pheasant flocks, and equine cases are indicators that Virginia may be at increased risk.

La Crosse (LAC) virus is transmitted by mosquitoes that breed only in tree holes and artificial containers of water. The presence of these breeding sites in close proximity to human populations increases the risk of disease. The virus is maintained by a cycle that involves mosquitoes and vertebrate hosts (squirrels and chipmunks). In Virginia, it is reported most often from southwestern counties. Children under 15 years of age are at greatest risk of illness from La Crosse and may develop seizures.

St. Louis Encephalitis (SLE) epidemics have occurred in the Midwest and southeast, but the virus is distributed throughout the lower 48 states. It has occurred sporadically in Virginia. The majority of infections are not clinically apparent. The elderly are at a higher risk of developing severe disease and death. SLE is maintained in nature through a mosquito-bird-mosquito cycle. SLE virus activity can be monitored using bird and mosquito surveillance, with monitoring of ecological and environmental changes.

West Nile virus (WNV) was first identified in the United States (U. S.) in 1999, in an epizootic outbreak among birds and horses and an epidemic of meningitis and encephalitis in humans in the greater New York metropolitan area. Throughout 2000-2001, avian mortality surveillance documented geographic spread to about half of the U.S. From 1999 through 2001, there were 149 cases of WNV human illness in the U. S. reported to the Centers for Disease Control and Prevention (CDC) and confirmed, including 18 deaths. In 2002, major epidemics of human WNV infection were detected in many parts of the U. S. The number of human cases far exceeded those reported from 1999 through 2001. Many states, including Virginia, detected human WNV infection for the first time in 2002. Through surveillance, human WNV infection was detected in over 4,000 persons, including 284 deaths, from 39 states and the District of Columbia. In 2003 the virus spread towards the West and major epidemics of human infection

were observed with the majority of cases reported from the Midwest and Southwest. In 2003, over 9,000 persons were reported as having West Nile infections, with 227 deaths, reported from 45 states including the District of Columbia. The majority of cases reported in 2003 were WNF (69% vs. 29% of WNND). It is believed that the peak of the 2003 WNV epidemic in the U. S. occurred in August - September and abated, as the weather became cooler and mosquito activity declined. Reduced levels of WNV human activity were observed in 2004. Only 2,470 cases of West Nile infection were reported. Nine hundred (37%) were reported as having WNND, 1,017 (41%) were reported as having West Nile fever (milder disease), and 553 (22%) were clinically unspecified. There were 88 deaths.

In 2002, between August and October, the CDC had received reports of patients with confirmed WNND diagnosed after receiving blood within one month of illness onset. All of the case-patients resided in areas of high WNV activity. Investigations confirmed that WNV can be transmitted through blood transfusion. In addition to these patients, investigations in Georgia and Florida have demonstrated transmission of WNV in four recipients of solid organs from a single organ donor. Transplacental transmission of WNV infection was also reported in 2002 and WNV was found in the breast milk of a nursing mother and implicated in transmission to an infant. Two laboratory workers were thought to be infected through percutaneous inoculation. Also in 2002, an investigation of two cases of febrile illness in turkey breeder farm workers lead to the observation that turkey breeder workers and turkeys had a high prevalence of WNV infection. Transmission of the virus in this situation has not been determined but the epidemiologic evidence suggests that the outbreak is related to occupational exposure. These various transmission mechanisms will have to be considered when doing human surveillance in Virginia.

VDH expanded its enhanced and active surveillance for arboviral infection in 2004 and will continue to maintain the quality and timeliness of reporting and be able to respond rapidly. An essential component of a suitable surveillance program for arboviral infection includes rapid and complete laboratory diagnosis of all suspect cases. Human surveillance is just one component of an effective arboviral surveillance program, and will be coordinated with mosquito, avian and mammal surveillance programs. Information from all of these programs will be used to determine the type of mosquito control that is needed in a community to prevent as many human cases as possible in Virginia.

Arboviral infections may be asymptomatic or may result in febrile illnesses of variable severity sometimes associated with central nervous system (CNS) involvement. When the CNS is affected, clinical syndromes such as aseptic meningitis, encephalitis, myelitis and neuritis may occur, which are clinically indistinguishable from similar syndromes caused by other viruses. Arboviral meningitis is characterized by fever, headache, stiff neck, and pleocytosis in cerebrospinal fluid. Arboviral encephalitis is characterized by fever, headache, and altered mental status ranging from confusion to coma with or without additional signs of brain dysfunction. Arboviral myelitis is often characterized by fever and acute bulbar or limb paresis or flaccid paralysis. Less common neurological syndromes can include cranial and peripheral neuritis/neuropathies.

Non-neuroinvasive arboviral disease, such as West Nile fever (WNF), is usually a non-specific, self-limited, febrile illness that generally occurs 2-6 days (range, 2-15 days) following the bite of an infected mosquito. Typical cases are characterized by the acute onset of fever, headache, arthralgias, myalgias, and fatigue. Maculopapular rash and lymphadenopathy generally are observed in less than 20% of cases. There is some indication that WNF is more severe and prolonged than originally reported. These more serious WNF cases are more likely to come to the attention of medical care providers and therefore be reported, but they represent only a small minority of all WNF cases.

Arboviral infection is one of more than 70 reportable diseases and conditions in Virginia. Physicians are required to report all suspect cases to local health departments (LHDs) in Virginia. However, physician reporting in general is not as reliable as laboratory-based reporting. Since most cases of arboviral infection are diagnosed based on clinical criteria and the absence of bacterial pathogens on microbial testing of cerebrospinal fluid (CSF), significant under-reporting of arboviral infection is likely.

Therefore, to ensure detection of an early or late human case enhanced passive surveillance for arboviral infection will be conducted by all jurisdictions in Virginia during November through June. Active surveillance will be implemented during peak months of mosquito activity and virus amplification (July through October).

II. Objective

Improve our ability to promptly detect and respond to a human case or outbreak by instituting swift and appropriately targeted control measures to prevent further cases.

III. Implementation Plan

A. Surveillance Activities for Arboviral Infection

There will be statewide, enhanced passive surveillance for neuroinvasive arboviral infection during the season when mosquitoes are least active (November through June) and active surveillance during the season when mosquitoes are most active and peak amplification of the viruses is occurring (July through October). Active surveillance can be implemented earlier if resources permit and arboviral activity intensifies in avian, mammal or mosquito populations in an area.

Non-neuroinvasive surveillance will consist of providing information to health care providers on the low probability of WNF leading to increased morbidity and the importance of seeking medical care should symptoms worsen. Medical care providers should reserve testing for those persons who have documented fever in the absence of a more likely explanation for the illness and symptoms that are severe enough to require medical oversight or hospitalization. Follow up on these cases by LHDs will be resource dependent and be of lower priority than neuroinvasive cases. Testing will be done by DCLS unless neuroinvasive cases deplete DCLS resources.

1. **Enhanced Passive Surveillance** - Recommended for all Virginia counties and cities from November through June for WNND.

   a. Alerting the medical community. Using information generated by the VDH Office of Epidemiology, the Centers for Disease Control and Prevention (CDC) and locally developed materials, LHDs should alert hospital infection control personnel and physicians regarding the importance of reporting suspected arboviral infection, the criteria for reporting and instructions for submission of appropriate laboratory specimens (see Attachment 2.A). Physicians should be encouraged to develop a high index of suspicion for arboviral infection in patients hospitalized with encephalitis or meningitis of unknown etiology. In addition, cases of suspected Guillain Barre syndrome, botulism, and muscle weakness or flaccid paralysis should have WNV infection as a rule out. Physician education materials should include the importance of determining if there is a history of donating or receiving blood or organs or if the patient is pregnant or breast-feeding.

   b. Commercial laboratory surveillance. LHDs will receive reports of sero-positive cases of WNV and other arboviruses tested by commercial laboratories from hospitals, physicians, DCLS and the Office of Epidemiology. Since WNV may cross-react with SLE and other closely related flaviviruses on commercially available serologic tests, cases that are reported as SLE- positive or some other arboviral disease based on serologic testing should be confirmed by DCLS. DCLS will perform highly specific IgM Microsphere Immuno Assays (IgM MIA) to detect IgM specific for WNV and SLE and IgM antibody capture enzyme-linked immunosorbent assays (MAC-ELISA) to detect virus specific IgM antibodies to EEE and LAC.. IgG ELISA will be used to identify SLE, EEE, LAC, and WNV-reactive antibody in IgM positive specimens. Specimens from patients with WNND and detectable levels of virus specific IgM and IgG will be tested for confirmation with a plaque reduction neutralization test (PRNT) performed either at DCLS or CDC. Reactive specimens from patients with WNF will be tested for confirmation with PRNT at DCLS as resources permit. Many asymptomatic and mildly ill patients who have been bitten by mosquitoes may ask their physicians to test them for WNV. Even if infected, those with mild symptoms are likely to recover completely without the need for any specific medications and laboratory testing for WNV is not necessary. Should these patients develop more severe symptoms, such as acute onset of fever, headache, arthalgias, fatigue, maculopapular rash, lymphadenopathy, confusion, lethargy, muscle

weakness/paralysis, severe headache, or stiff neck, appropriate specimens should be submitted to the DCLS for WNV testing.

2. **Active Surveillance -** The first activity (a.) should be conducted from July through October, or earlier if resources permit and arboviral activity intensifies in an area. The other activities are optional for LHDs as resources permit. Viral neuroinvasive disease should be included as an event LHDs monitor through syndromic surveillance systems.

   a. Active surveillance by weekly contact. LHDs should contact key medical staff (e.g., infectious disease, neurology or intensive care subspecialists) at acute-care hospitals to ask about potential cases of arboviral infection and assure that appropriate laboratory specimens are obtained on all suspect cases and sent to DCLS for arbovirus testing. In addition, cases of suspected Guillain-Barre syndrome, botulism, and muscle weakness or flaccid paralysis should have WNV infection as a rule out.

   b. Laboratory-based surveillance at hospitals (optional). LHDs will ask laboratory staff to store all CSF samples that have parameters suggestive of a viral cause of infection of unknown etiology (e.g., increased protein, pleocytosis and negative bacterial gram stain and culture). Samples should be transported to the DCLS weekly where they will be screened for arboviruses by IgM MIA and/or MAC-ELISA as resources permit and should be cleared with the DCLS before being implemented. This laboratory-based system will provide a back-up to ensure that viral neuroinvasive cases that are not reported by clinicians are tested for arboviruses.

   c. Retrospective surveillance (optional). Patients discharged with a diagnosis of encephalitis (and aseptic meningitis as resources permit) of unknown etiology will be identified. The VDH Office of Epidemiology will work with LHDs to have hospitals search their databases for patients discharged with specific ICD codes. Hospital laboratory directors will be contacted to determine if sera or CSF are available on identified suspect cases and, if so, arrangements will be made for testing at the DCLS. Patients without available clinical specimens will be contacted to obtain convalescent sera.

3. **Non-traditional Arboviral Surveillance Methods** (Potential alternative options to be considered by jurisdictions if resources are available.) Such activities should be undertaken in consultation with the Office of Epidemiology because they may be useful for other diseases and conditions.

a. Monitor existing clinical datasets (911 data, emergency departments, managed care visits, nurses' hotlines) to detect increases in milder illnesses that may represent infection with WNV (e.g., fever/rash or fever/lymphadenopathy).

b. Establish surveillance for gastrointestinal disease in children that could indicate LAC infection, especially in areas endemic for LAC.

c. Conduct laboratory surveillance to monitor volume of tests requested for other causes of encephalitis (e.g., herpes simplex).

B. Surveillance Guidelines for Human Arboviral Infection

1. Cases of arboviral disease are classified either as neuroinvasive or non-neuroinvasive, according to the following draft criteria (Health Departments will be notified if the case definition changes):

   a. **Neuroinvasive disease** requires presence of fever and at least one of the following, as documented by a physician and in the absence of a more likely clinical explanation:

      - Acutely altered mental status (e.g., disorientation, obtundation, stupor, or coma), or
      - Other acute signs of central or peripheral neurologic dysfunction (e.g., paresis or paralysis, nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions, or abnormal movements), or
      - Pleocytosis (increased white blood cell concentration in cerebrospinal fluid [CSF]) associated with illness clinically compatible with meningitis (e.g., headaches or stiff neck).

   b. **Non-neuroinvasive disease (West Nile Fever)** requires, at minimum, the presence documented fever, measured by the patient or clinician, the absence of neuroinvasive disease (above), and the absence of a more likely clinical explanation for the illness. Involvement of non-neurological organs (e.g., heart, pancreas, liver) should be documented using standard clinico-laboratory criteria.

2. Additional WNV Surveillance Issues

   a. Evidence of organ transplant and blood transfusion transmission of WNV makes it important for LHDs to rapidly determine if any human cases of probable or confirmed WNV infection had a organ transplant or blood transfusion within the four weeks prior to

illness onset or was a blood donor two weeks prior to illness onset. The VDH Office of Epidemiology should be notified immediately of potential transplant/transfusion related cases. A trace back investigation of the cases will involve the CDC and the Food and Drug Administration (FDA).

b. Evidence of intrauterine and possible breast milk transmission makes it important to identify and monitor pregnant and nursing mothers if WNV infection is suspected. The VDH Office of Epidemiology should be contacted about such cases and efforts should be made to enroll pregnant women in a CDC study (See Attachment 2.B).

c. Evidence of laboratory-acquired infections and non-mosquito exposure to WNV-infected birds makes it important to determine if there are any human cases that may result from occupational exposure. The VDH Office of Epidemiology should be contacted about these cases if occupational exposure is suspected.

d. WNV infected patients exhibiting acute flaccid paralysis should have the screening form (See Attachment 2.C) completed and copies faxed to CDC and VDH Office of Epidemiology.

C. Laboratory Testing for WNV

1. Although suspect cases can be reported to LHDs or the VDH Office of Epidemiology using the Epi-1 reporting form or the initial case report form (See Attachment 2.D), if enhanced passive or active surveillance has been initiated it should result in rapid and direct communication between medical care providers and the LHDs. LHDs will screen reports to assess that the clinical presentation meets the case criteria for WNND or WNF and therefore, for testing by the DCLS. As part of enhanced passive or active surveillance, LHDs should insure that hospitals and laboratories have on hand and are aware of the latest surveillance criteria and information on how to submit appropriate diagnostic specimens for testing at the DCLS.

2. Since a negative reverse transcriptase polymerase chain reaction (RT-PCR), IgM MIA, or MAC-ELISA test on a specimen taken soon after illness onset (<10 days) does not rule out arboviral infection, convalescent sera are needed to definitively determine if WNV infection is present or absent. Therefore, LHDs will have to insure that convalescent sera are obtained on all suspected case-patients with encephalitis of unknown etiology, if acute sera or CSF obtained <10 days after illness onset is negative for WNV. It is important that paired acute- and convalescent-phase serum samples be submitted to insure accurate interpretation of the

serologic tests

3. The DCLS will perform all testing for WNV, including IgM MIA and MAC-ELISA on sera and CSF, IgG ELISA on IgM positive sera, and RT-PCR on post mortem tissue.

4. Health care providers should be informed that appropriate specimens for testing include:

   a. Sera - Appropriately timed acute and convalescent sera for testing by IgM MIA (WNV and SLE), and IgG ELISA

   b. CSF - Testing by IgM MIA or viral isolation

   c. IgM-positive acute sera should be confirmed by convalescent sera (IgM MIA, IgG ELISA and PRNT)

   d. Brain tissue – Real-time RT-PCR and viral isolation.

5. LHDs need to encourage physicians and laboratories to complete all essential information on the laboratory submission forms or to complete it themselves by contacting appropriate parties, including the patient or patient's family, if necessary. Accurate interpretation of serological findings requires knowledge of the clinical history. For human specimens, it is important that the following data accompany specimens submitted for serology before testing can proceed or results can be properly interpreted and reported:

   a. Symptom onset date (Critical information that frequently is not documented on the initial case report form)

   b. Date of sample collection

   c. Unusual immunological status of patient (immunosuppression)

   d. Current address and travel history in Flavivirus-endemic area

   e. History of prior vaccination against Flavivirus disease (Yellow fever, Japanese Encephalitis, or CE)

   f. Brief clinical summary including suspected diagnosis

6. Patient information and laboratory data will be shared between the VDH Office of Epidemiology and LHDs in person, via telephone and facsimile or, when available, on a secure e-mail system to facilitate case surveillance and timely reporting of laboratory results back to LHDs.

7. In the event that acute specimens (obtained within 10 days of illness onset) are negative by ELISA testing, laboratory diagnosis of WNV will require that a follow-up (convalescent) blood sample be obtained 14-21 days after the acute specimen to evaluate for the presence of convalescent antibody to the virus. Since most patients will have been discharged from the hospital, LHDs will need to facilitate the collection and submission of convalescent blood specimens on all WNND suspect case-patients who have inconclusive or indeterminate initial test results.

8. LHDs will work with hospitals and physicians to encourage testing for those patients that meet the criteria for WNND. Patients with symptoms of WNF may be tested at DCLS for WNV infection as resources permit (e.g., fever and headache, fever and rash, fever and lymphadenopathy). Patients with no symptoms (e.g., persons with a recent mosquito bite but no acute symptoms) do not need to be tested for WNV.